Evidence for a Similar Mode of Action for B(a)P in Mouse and Human Skin

B(a)P can either induce tumors after a single topical application to mouse skin followed by repeated tumor promoter treatment or when given repeatedly in a complete carcinogenesis protocol (DiGiovanni, 1992; Abel et al, 2009). After topical application to mouse skin, B(a)P is metabolically activated to diol-epoxides leading to formation of covalent DNA adducts, especially the (+)-anti-BPDE-dGuo adduct (DiGiovanni, 1992). The formation of this DNA adduct leads to mutations in the *Ha-ras* gene of keratinocyte stem cells that represents an initiating event for tumor development in this tissue (DiGiovanni, 1992; Abel et al, 2009). Experimental evidence exists to show that B(a)P is metabolically activated to produce similar types of DNA adducts in human skin. In this regard, Lehman et al (1989) showed that human skin epithelial cells in culture treated with B(a)P produced the 7,8-diol metabolite and DNA adducts derived from anti-BPDE. Watson et al (1989) showed that epidermal DNA from human skin explants treated with radiolabeled B(a)P had similar DNA adduct profiles to those seen in both mouse epidermis and epidermal DNA samples from mouse skin explants. The major adduct was identified in all three DNA samples as (+)-anti-BPDE-dGuo. In addition, Zhao et al (1999) showed that treatment of a reconstituted human skin equivalent model with B(a)P led to formation of DNA adducts derived from (+)-anti-BPDE and also led to the upregulation of c-fos and p53 proteins. The level of p53 protein has also been shown to increase in mouse epidermis in association with the formation of BPDE-DNA adducts (Serpi and Vahakangas, 2003). Brinkman et al (2013) also recently demonstrated that B(a)P was metabolized to diol-epoxide metabolites in several different models of human skin and showed that tetraols derived from anti-BPDE could be readily detected in samples from all of the model systems evaluated, including human skin explants. B(a)P was metabolized to genotoxic metabolites in both NHEKs and a reconstituted skin equivalent system (EpiDermFT) in this study. Finally, in a study of atopic dermatitis patients treated with coal tar, Rojas et al (2001) demonstrated the presence of anti-BPDE-DNA adducts in skin of these patients. The levels of anti-BPDE-DNA adducts in coal tar treated patients was also modulated by polymorphisms in the myelo-peroxidase gene. In conclusion, the available data suggest a similar mutagenic mode of action for B(a)P in both mouse and human skin epidermis.

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